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EDITORIAL

T-cells in myocardial infarction: Culprit instigators or mere effectors?

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Abstract

Immune system activation and dysfunction characterize the early phase of reperfusion after a myocardial infarction (MI). Despite initially neglected, adaptive immunity has been recently showed to play an important role in this setting. In fact, the immune system can recognize sequestered antigens released by the necrotic tissue, initiating a deleterious autoimmune vicious circle leading to worse outcome. In their recent work, Angelini *et al* shed the light on a new feature of post-MI which involves two "old players" of post-ischemic myocardial injury: CD31 and matrix metalloproteinase (MMP)-9. Specifically, the authors showed that an enhancement of MMP-9 release could determine the cleavage of inhibitory CD31 from CD4+ T-cells surface in patients with Acute Coronary Syndromes (ACS). These findings open the room for new studies investigating the role of MMP9 in other pathological processes associated with a reduction of CD31 functionality, such as plaque instability and rupture. Of interest, in the case of a causative role for CD31 shedding in ACS would be confirmed, there might be a potential role for the administration of CD31 protein or analogue compounds to blunt post-ischemic cardiac inflammation and improve ACS outcome.

Key words: Matrix metalloproteinase; Lymphocytes; Autoimmunity; Inflammation; Myocardial infarction; Adaptive immunity

Core tip: CD31 and matrix metalloproteinases (MMP)-9 are known mediators that are upregulated during reperfusion after cardiac ischemia. By inhibiting T-cell

receptor-dependent lymphocyte activation, the functional CD31 could reduce post-ischemic inflammatory response; while MMP-9 is deeply involved in inflammatory cell recruitment and myocardial remodeling. A recent paper published in European Heart Journal linked these mediators by showing CD31 cleavage to be MMP-9 dependent in patients with acute coronary syndromes (ACS). Whether this process is causative of ACS or rather its effect still needs to be clarified.

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INTRODUCTION

Acute Coronary Syndromes (ACS)-including unstable angina and myocardial infarction (MI) are the most detrimental atherosclerosis-related complications being the leading causes of mortality worldwide and a considerable source of morbidity[1]. Although outstanding leap forwards of primary and secondary prevention measures, the issue of the residual risk for ischemic complication is still unsolved[2]. Also, it is now well-recognized that after a prompt reperfusion, as it is the case of vast majority of patients suffering from MI, the ischemic hearts need to face an additional damage directly induced by the re-establishment of blood flow itself[3]. The role of innate immunity in the determination of both residual risk and ischemia/reperfusion injury has been studied from decades and is now better established[4-6]. The adaptive immune system (*i.e.*, T-cells and B-cells) have only recently come into focus. Indeed, lymphocytes' ability to react only against specific non-self-antigens, as opposed to the reactivity against non-specific danger signal showed by innate immunity, excluded these mediators from the list of "guilty" parties for a long time. Only recently, the recognition of a role for the release of sequestered antigens from the necrotic tissue in the progressive diversification of autoreactive lymphocytes (*i.e.*, epitope spreading) shed the light on the potential involvement of adaptive auto-reactivity in the determination of post-MI outcome[7]. After an ACS, the necrotic heart tissue releases several danger-associated molecular patterns (DAMPs) together with cardiac intracellular proteins[8,9]. In this highly inflamed micro-environment, cardiac antigens can be recognized by autoreactive lymphocyte clones and trigger autoimmunity processes. Afterward, the same immune-mediated tissue injury supplies the amount of autoantigens necessary to maintain the auto-reactivity thus sustaining the dysfunctional immune cardiac process[9]. This editorial refers to the outstanding research article entitled "matrix metalloproteinases-9 might affect adaptive immunity in non-ST segment elevation ACS by increasing CD31 cleavage on CD4+ cells", recently published by Angelini *et al*[10] in European Heart Journal.

T-CELLS AND ACS

Although several studies have implicated T-cells in the pathophysiology of ACS, the knowledge about their specific role is still elusive. Considering the heterogeneity of T-cell subsets and the quickly evolving local and systemic environment after ACS, a tight regulation of rapidly changing T-cell phenotypes with regulator or effector functions is likely[11]. Experimental evidence highlights infiltrating T-cells as effector lymphocytes which have been antigen-restricted and primed in the heart-draining lymph nodes. Of interest, after ACS, particular subsets of pro-inflammatory CD28- CD4+ and Th17 lymphocytes are released in the blood stream and produce large amounts of interferon-γ and IL-17: Detrimental cytokines with known ability to increase cardiomyocyte death, fibroblast proliferation and pro-fibrotic gene expression[12-14]. Not only detrimental T-cells with effector functions are increased after ACS but they also display dysfunctional features. Indeed, they overexpress CD40 ligand in this way being more easily activated by antigen presenting cells[15]. Furthermore, a direct cytotoxic effect of infiltrating autoreactive CD8+ T-lymphocytes with specificity towards cardiac myosin has been described[16]. To further potentiate the detrimental role of T lymphocytes in the setting of MI, the raise of pro-inflammatory lymphocyte subsets is accompanied by a reciprocal reduction in CD4+CD25+Foxp3+ regulatory T-lymphocytes with a beneficial cardiac protective role[17].

MMP-9 AND CD31: A DANGEROUS ASSOCIATION

Post-transcriptional CD31 modifications showed capacity to affect normal T-lymphocyte function. Indeed, CD31 (also known as platelet endothelial cell adhesion molecule-1) was shown to regulate T lymphocyte activity through the inhibition of T cell receptor (TCR) signalling[18]. Of interest, CD31 extracellular domain is shed from the lymphocyte surface during ACS and this contributes to the over activation of adaptive immunity[19]. In their recent article, Angelini *et al*[10] added one more piece to this puzzle by showing matrix metalloproteinase (MMP)-9 to be involved in CD31 cleavage in lymphocytes from ACS patients. Firstly, they confirm CD31 shedding to be a specific feature of lymphocytes in ACS, as compared to samples from healthy subjects but also patients with stable angina (SA). Then, the authors demonstrated *in vitro* that down-regulation of the functional CD31 domain in ACS is associated with TCR activation and is led by post-transcriptional mechanisms since post-stimulation levels of CD31 mRNA were similar in ACS and SA cells. Finally, after observing CD31 to be a possible substrate for MMP-9 by using an dedicated software predicting novel substrates and their cleavage sites, the auth-

ors show lymphocytes from ACS patients to produce higher enzyme levels after stimulation and CD31 active domain to be preserved by MMP-9 inhibition. Based on these results, the authors propose a new sequence of events that might characterize ACS onset in which the increased release of MMP-9 causes CD31 cleavage, thus affecting TCR-dependent T-cell activation and causing T-cell hyperactivity[10].

PERSPECTIVES

Angelini *et al*[10] added knowledge to the field of dysfunctional adaptive immunity in ACS. At the same time, they raise new appealing questions. In particular, CD31 is known to mediate also endothelial-endothelial interactions, thus allowing the constitution of the continuous and protective intimal cell monolayer[20]. Now, further investigations are advisable to assess whether the inflammation-induced overproduction of MMP-9[21] could reduce these interactions and potentially contribute to endothelial erosion and plaque instability. Under this point of view, CD31 was previously described to target macrophage activation, as well as cytokine and chemokine release within atherosclerotic plaques and aneurysmal peri-aorta[22]. Also, it would be of interest to show CD31 modifications in lymphocytes to take act before ACS onset. In general, this is a very common weakness of studies focused on cellular phenotype during ACS due to the requirement of intact cells for fluorescent-activated sorting which does not allow sample storage before the dosage. Animal studies could help in assessing this causal connection.

Given the fact that CD31 protein or analog molecules are already available[23], answering these questions could point out CD31 replacement as a potential therapeutic approach to blunt inflammation and modulate tissue damage in acute cardiovascular diseases (such as MI and stroke) that are characterized by an impaired adaptive immunity.

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